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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,109	11/19/2003	Ram I. Mahato	T8948.CIP.2	7310

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 11/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/717,109	MAHATO ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received on 9/11/06.

This application is a continuation in part of 10/083,861 which is a continuation in part of 09/662,511, now US 6,696,038.

Claims 1-27 are pending and under consideration in this Office Action.

A terminal disclaimer over US Patent 6,696,038 was received and approved. Accordingly the double patenting rejections of claims 1-21 and 22-27 are withdrawn.

This Action is NON-FINAL due to new grounds of rejection not necessitated by Applicant's amendments.

Claim Objections

Claim 27 stands objected to because "disteroyl" is misspelled. Did Applicant intend "distearoyl"?

Applicant's amendments overcame the other objections set forth in the previous Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 14, 15, and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4 and 15 are indefinite because the metes and bounds of "cholesterol derivatives" and "fatty acid derivatives" are unclear.

Claim 14 is indefinite because it recites "the covalent bond" without proper antecedent basis. Claim 14 depends from claim 12 in which there appear to be 2 antecedents for "the bond". Claim 12 requires each of the lipid and the hydrophilic polymer to be independently and directly linked to the PEI by a covalent bond. As such claim 12 provides antecedent basis for two distinct covalent bonds, and one of skill in the art cannot know if claim 14 refers to one, the other, or both of them.

Claim 27 is indefinite because it is unclear what is intended by "disteroyl-, palmitoyl-, myristoylphosphatidylethanolamine." If this is supposed to reflect a diacylgylcerol phospholipid, then Applicant is reminded that such compounds may have only two acyl groups.

Response to Arguments

Applicant's arguments filed 9/11/06 have been fully considered but they are not persuasive. Applicant asserts at page 6 of the response that the claims were amended to address the concerns raised by the Examiner. This is unpersuasive because the issues set forth above concerning claims 4, 15 and 27 remain. Note that the rejection over claim 14 is new.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6, 7, 9, 12, 13, 15, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Puckett et al (US Patent 5,393,335, issued 2/28/95).

Puckett teaches a lubricant consisting of C2-C18 fatty acids linked by amide bonds to polyethyleneimine of molecular weight from 800 to 50,000 Da. See column 3, lines 12-18. Puckett does not explicitly teach whether or not the lubricant is biodegradable, however it has the same physical structure as that claimed in the claims. "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or In re Best, 195 USPQ 430, 433 (CCPA 1997).

Claim 6 is included in this rejection because an arbitrary fraction of the PEI can be considered to be the hydrophilic polymer, while the remainder can be considered to be the polycation. Claims 12 and 17 are included in the rejection for a similar reason. One half of the PEI can be considered to be a polycation that is attached at either end to a lipid and to a hydrophilic polymer (i.e. the other half of the PEI). As a result the molar ratio of PEI to hydrophilic polymer would be 1:1. Because the lipid is attached along the length of the PEI molecule, the molar ratio of PEI to lipid would depend on how much of the PEI was considered to be polycation, and how much was considered to be hydrophilic polymer.

Thus Puckett anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cullis et al (US Patent 6,852,334) in view of Godbey et al (J. Contr. Rel. (1999) 60: 149-160).

Cullis taught cationic-polymer-lipid conjugates of the general formula A-W-Y, wherein A is a lipid moiety that acts as a lipid anchor, W is a hydrophilic polymer, and Y is a polycationic moiety. See column 2, lines 43-51. The lipid can be a diacylglycerol comprising fatty acyl chains of 2-30 carbons. See column 4, lines 38-41. The hydrophilic polymer can be PEG of 250-7000 Da. See column 13, lines 11-16. The polycationic moiety can be a linear or branched polyamine (column 13, lines 21-26), and can have an attached targeting antibody. See column 14, lines 6, 7, 10, and 14. The complexes are intended to be used for the delivery of nucleic acids. See abstract and e.g. column 15, lines 55-63. The components of the conjugate are joined by amid or ester bonds, see paragraph bridging columns 13 and 14. Helper lipids such as DOPE are used in the conjugate compositions. See entire document, e.g. column 3, lines 49-50.

Although Cullis suggested linear or branched polyamines as polycations, Cullis did not explicitly teach the use of PEI as a polycation.

Godbey taught that PEI is a polyamine polycation that will spontaneously adhere to and condense DNA to form complexes that are readily endocytosed by cells, and that PEI buffers endosomal pH, thus allowing cytoplasmic release of DNA prior to lysosomal degradation. See page 157, column 2, first full paragraph. Godbey taught that the optimal molecular weight was about 25 kDa, and that both linear and branched forms were used. See page 150, column 2, lines 6-11, and page 153 at lines 1-11 of paragraph bridging pages 153 and 154.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use PEI as a polycation in the invention of Cullis. One would have been motivated to do so in view of the art recognized utility of PEI as a nucleic acid condensing and delivery agent, and the fact that the compositions of Cullis are intended for use in delivering nucleic acids. The ratios of PEI to hydrophilic polymer and lipid, and the ratio of lipopolymer to targeting moiety, and the N/P ratios of nucleic acid/conjugate complexes are considered to be result effective variable that are routinely optimized by those of ordinary skill in the art.

Claims 12-21, 24, and 25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Epand et al (US Patent 5,283,185, issued 2/1/94) in view of Ogris et al (Gene therapy (1999) 6: 595-605).

Epand taught methods and lipopolymeric compositions for transferring nucleic acids into cells. See abstract, claims 1 and 10, and compound XV, described at column 9, lines 45-58. Lipopolymeric compound XV is formed by mixing cholesteryl

chloroformate with PEI 600. The resulting reaction chemistry is identical to that taught in the instant application, and results in the formation of a lipopolymer with cholesterol covalently bound to PEI via an ester linkage. Compare Fig. 1 of the instant application with Fig. 3 of Epand. The composition may comprise a DOPE helper lipid in a 1:1 ratio with the cationic lipopolymer. See Table I at column 12, and column 12, lines 58-61. Epand teaches that the charge ratio of lipopolymer to nucleic acid is a result effective variable. See column 13, lines 6-11, and Fig. 5.

Epand did not teach PEI covalently modified with a biocompatible hydrophilic polymer or a targeting ligand.

Ogris taught DNA/transferrin/PEI/PEG complexes in which PEG and transferrin were independently covalently attached to primary amines of PEI. The PEG has a molecular weight of 5000 D. Approximately two thirds of the primary amino groups of PEI remained unmodified. See abstract; and paragraph bridging pages 595 and 596. Ogris taught successful delivery to tumor cells in mice by systemic administration of the complexes.

It would have been obvious to one of ordinary skill in the art the time of the invention to graft PEG to the branched lipopolymer of Epand et al, as well as to attach a targeting ligand such as transferrin. One would have been motivated to do so because Ogris teaches that covalent attachment of PEG to DNA/PEI complexes improves DNA delivery in vivo. See abstract and first paragraph on page 595, column 1. It would have been similarly obvious to optimize the N/P ratio of a nucleic acid complex comprising

the lipopolymer, as well as the amount of targeting ligand incorporated into the complex, as each of these will clearly affect the performance of the complex.

Claims 12-15, 17-21, 24, and 25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Epand et al (US Patent 5,283,185, issued 2/1/94) in view of Godbey et al (J. Contr. Rel. (1999) 60: 149-160).

Epand taught methods and lipopolymeric compositions for transferring nucleic acids into cells. See abstract, claims 1 and 10, and compound XV, described at column 9, lines 45-58. Lipopolymeric compound XV is formed by mixing cholesteryl chloroformate with PEI 600. The resulting reaction chemistry is identical to that taught in the instant application, and results in the formation of a lipopolymer with cholesterol covalently bound to PEI via an ester linkage. Compare Fig. 1 of the instant application with Fig. 3 of Epand. The composition may comprise a DOPE helper lipid in a 1:1 ratio with the cationic lipopolymer. See Table I at column 12, and column 12, lines 58-61. Epand teaches that the charge ratio of lipopolymer to nucleic acid is a result effective variable. See column 13, lines 6-11, and Fig. 5.

Epand did not teach PEI covalently modified with a biocompatible hydrophilic polymer or a targeting ligand.

Godbey taught that PEI may be covalently modified with PEG for the purpose of extending its half life in vivo. See paragraph bridging columns 1 and 2 on page 153. Additionally, Godbey teaches that PEI has been coupled to a variety of ligands for the purpose of cell targeting, including galactose and transferrin, and notes that ligands

which have been successfully used in poly(L-lysine)/DNA complexes should be useful in PEI/DNA complexes as well. Such ligands include low density lipoprotein. See paragraph bridging pages 154 and 155. Godbey reviewed the use of PEI in gene delivery methods, and noted that PEIs ranging in molecular weight from about 8000 to about 1,000,000 are useful for gene delivery. See page 121, paragraph bridging columns 1 and 2; and Fig. 2 on page 151. Godbey also taught that the molecular weight of PEI in such complexes is a result-effective variable, and that the ratio of PEI amine to DNA phosphate is also a result-effective variable. See page 153, column 1, second and third full paragraphs; and lines 1-6 of the paragraph bridging pages 153 and 154.

It would have been obvious to one of ordinary skill in the art the time of the invention to covalently modify the PEI of Epand with PEG in order to increase its half life in vivo, and to attach targeting ligands to PEI in order to improve the specificity of nucleic acid delivery. It would have been similarly obvious to optimize the N/P ratio of a nucleic acid complex comprising the lipopolymer, as well as the amount of targeting ligand incorporated into the complex, as each of these will clearly affect the performance of the complex.

Response to Arguments

Applicant's arguments filed 9/11/06 have been fully considered but they are not persuasive.

Applicant argues at pages 8 and 9 of the response that the method of PEI coupling to cholesterol and PEG in the instant application is different from that of the cited methods for coupling PEI to cholesterol. This is unpersuasive because Applicant is arguing limitations that are not in the claims. The rejected claims embrace any biocompatible lipopolymer comprising PEI, a lipid, and a biocompatible hydrophilic polymer wherein the lipid and the hydrophilic polymer are directly and independently joined to the PEI backbone by covalent bond, regardless of the synthesis technique.

Applicant argues at page 9 of the response that one of skill in the art would not be motivated to combine Ogris with Epand because the degree of PEG incorporation in the TfPEI/DNA complexes of Ogris was not quantified, so the true characteristics with respect to PEG incorporation are unclear. This is unpersuasive because it is a matter of opinion that is not supported by evidence of that one of skill in the art would have required quantification of PEGylation prior to combining the teachings. On the other hand Ogris showed objectively that PEGylation of the complexes improved DNA delivery in vivo, see abstract. It seems clear that one of skill in the art would have been motivated to obtain the same advantage when using the invention of Epand, and would have PEGylated the complexes of Epand similarly, or simply added the cholesteryl moiety to the PEI of Ogris. Applicant asserts that the biological data of Ogris "is confounding where the PEGylation appeared to have improved pharmacokinetics but failed to preclude particle aggregation and in vivo toxicity under specific conditions." This is unpersuasive. Applicant failed to point to any passage in Ogris that showed in vivo toxicity of the PEGylated product, or aggregation of particles. In contrast, the

abstract of Ogris disclosed a decrease in toxicity as a result of PEGylation, and Fig. 3 of Ogris showed a decrease in the rate of aggregation of the PEGylated product (relative to non-PEGylated) over time. Furthermore, Applicant has failed to show that any relative toxicity or aggregation characteristics of the PEGylated product of Ogris are greater than those of the non-PEGylated product such that one of ordinary skill would not be motivated to PEGylate the product of Epand.

At pages 9 and 10, Applicant presents arguments as to why the Ogris method "could not teach the material described in the present invention." Essentially, Applicant questions whether or not Ogris actually achieved PEGylation of TfPEI primary amine groups. This doubt appears to be based on a sentence in Ogris that states "the ninhydrin assay was found to give the same results with free or DNA bound PEI conjugates". This sentence is interpreted by Applicant to mean that the same amount of PEI PEGylation was observed whether or not the PEI was complexed with DNA. Applicant argues that this should not be the case because DNA should bind to positively charged amine groups and interfere with their PEGylation. Applicant also argues that the ninhydrin assay conditions (95° C) could lead to dissociation of DNA from the PEI, thereby uncovering primary amines for the ninhydrin reaction and confounding the results. Applicants arguments are unpersuasive, for several reasons. First, they do not show that PEGylation of the complexes could not have occurred. At best they show that the quantification of Ogris may not have been accurate. Second, the Ogris article appeared in *Gene Therapy*, which is a peer reviewed and edited publication. As a result, the Ogris article was subject to review by referees of skill in the art , and its

conclusions constitute actual evidence that must be given more weight than Applicant's opinions that lack supporting evidence. Finally, the Ogris reference must be considered as a whole, and Ogris clearly attempted to PEGylate TfPEI, and reported a variety of results that are consistent with PEGylation, including stabilization of complexes in water, reduced surface charge of complexes, reduced plasma mediated aggregation of complexes, reduced interaction of plasma proteins with complexes, and increased stability of complexes in blood and plasma, and increased. See Figs 1-4 and 7. Applicant has provided no explanation of how these results were obtained if PEGylation did not occur. The simplest explanation is that it did occur.

At page 11, Applicant argues that Ogris discourages direct PEGylation of PEI, teaching away from the synthesis scheme of the instant application. This is unpersuasive because the rejected claims embrace any biocompatible lipopolymer comprising PEI, a lipid, and a biocompatible hydrophilic polymer wherein the lipid and the hydrophilic polymer are directly and independently joined to the PEI backbone by covalent bond, regardless of the synthesis technique.

Regarding the Godbey reference, Applicant argues that Godbey fails to teach covalent attachment of PEG to cholesterol, or targeted ligand-linked PEI. This is unpersuasive. Godbey was not relied upon to teach covalent attachment of PEG to cholesterol. Godbey was relied upon to teach that PEI may be covalently modified with PEG for the purpose of extending its half life in vivo. See paragraph bridging columns 1 and 2 on page 153. Furthermore, Godbey taught that PEI has been coupled to a variety of ligands for the purpose of cell targeting, including galactose and transferrin,

and notes that ligands which have been successfully used in poly(L-lysine)/DNA complexes should be useful in PEI/DNA complexes as well. Such ligands include low density lipoprotein. See paragraph bridging pages 154 and 155.

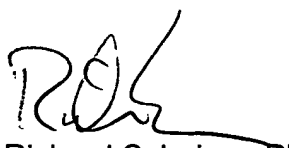
For these reasons the rejections are maintained.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Peter Paras, can be reached at (571) 272-4517. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.



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